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Via courier:
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Date 06.07.2004
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Draft Guidance for Industry:
Drug Substance – Chemistry, Manufacturing, and Controls Information

Docket No. 2003D-0571

Dear Sir/Madam

Merck KGaA, Germany is a manufacturer of active ingredients for drug products since 1827. Today Merck is operating in the business sectors Pharmaceuticals, Chemicals and Laboratory Distribution organized in different divisions. As a pharmaceutical company, Merck KGaA develops and markets prescription drugs to satisfy unmet medical needs in large patient populations. We supply customers throughout the world including the USA.

Therefore we are affected by the "Draft Guidance for Industry:
Drug Substance – Chemistry, Manufacturing, and Controls Information".

We appreciate very much the opportunity to provide comments on this draft guidance for industry. Please find the comment attached. It has been submitted already as electronic comment with the temporary no. 3604.

Sincerely,
Merck KGaA, Germany

i.V.

Dr. Stein

i.A.

Dr. Büttgenbach

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Merck KGaA, Germany Comments on Guidance for Industry: Drug Substance, Chemistry, Manufacturing and Controls Information

Docket No. 2003D-0571

Merck KGaA is pleased to provide comments on the recently issued Guidance for Industry.

We appreciate the implementation of this Guidance as it revises the -Guideline for submitting supporting documentation in drug applications for the manufacture of drug substances- February 1987 and as it adopted the requirements of the CTD. For support and further improvement of the guidance Merck KGaA offers the following comments in a constructive manner.

General Comments:

1. The requirements in the detailed documentation of the quality of the drug substance are in general contradiction to „Pharmaceutical cGMPs for the 21th Century: A Risk-Based Approach" of the FDA.

2. Many requirements are inconsistent to the ICH Guide Q7A "GMP for APIs" to which FDA are committed.

3. Attachment 1: **API Starting materials for synthetic drug substances: We recommend that this attachment should be reviewed and revised focusing on a risk and scientific based approach. The presented API Starting Material (API SM) concept is seen by the pharmaceutical industry worldwide as an additional significant regulatory burden.** From our perspective the currently proposed selection criteria for API SM are defined in a too detailed manner. In a science based approach API SM`s should be defined at a step where these are fully characterized to ensure suitability for the intended use. A more detailed analysis if the API SM is properly defined should be conducted in a case-by-case assessment. **Therefore a broad**

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definition of the API SM should be developed in accordance with the ICH-requirements (e.g. M4Q, Q7A). Additionally we recommend to follow the decision tree already published by PhRMA in Pharmaceutical Technology, issue February 2003. Key aspects in the definition of an API SM should consider the following issues (instead of those described in the draft guidance like propinquity, complexity of structure etc):

- Significant structural fragment incorporated into the API structure (see Q7A)
- Specification is appropriate to ensure the quality and safety of an API
- Well characterized (not necessarily isolated and purified)
- Appropriate analytical methodology for Quality Control QC is used / the use of advanced analytical techniques should be supported
- Impact of API-SM quality on API quality is known and controlled (it is important of any impurity is known, fully controlled and toxicological qualified; it is not important if the API SM or another intermediate is the origin of any impurity)
- Purification sequence is part of the API synthesis. Process should be developed and optimized in order to guarantee adequate downstream purification.
- Stability is understood, if applicable.

Attachment I, Chapter II - Documentation: should be revised and structured in accordance with chapter I under the consideration of the above-mentioned key aspects.

We recommend the following Text for Attachment I - Documentation: "API Starting materials should be fully characterized to ensure suitability for intended use, and the possibility of transferring impurities from the starting material to the final active substance should be discussed. For API SM complete specifications should be provided, including an impurity profile. Impurities present in an API SM may be carried through the synthesis/process unchanged or as derivatives, and should therefore be controlled in the API SM by appropriate acceptance criteria with suitably validated methods. Acceptance criteria should be established by the applicant based on evaluation of the fate of impurities present in the API SM, when subject to the normal synthesis/process. Acceptance criteria for accepting or rejecting batches should be indicated. The control of API SMs should be designed to detect isomeric or other impurities that are potentially reactive and be carried through to the final product of the synthesis. – Reference to ICH Q2A + Q2B, Q6A" (see EC Guide CPMP/QWP/130/96).

4. We recommend to adapt the requirements of semi synthetic drug substance to those of synthetic drug substance, because there is no difference in the synthesis after the API SM. A broad interpretation of the requirements regarding semi synthetic drug substances may cause problems in any synthesis in which -at any point- material of plant/biological origin has been used. Therefore a more detailed Quality Control testing of such API SM may be necessary.

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5. The introduction of the new definition of an *API starting material for application purposes* leads in conjunction with the requirement for the commercial availability to an extension of the detailed description of the manufacturing process. This leads to a big increase in change control in the production although GMP is not required. The new criterion "significant non-pharmaceutical market" for API SM is in contradiction to the request for high purity of the material. The parameter "Propinquity" leads to the requirement of several reaction steps after the introduction of the API SM. This does not reflect on the risk of additional impurities related to the chemical reaction itself.

6. The requirements in drug substances from synthetic synthesis and from biological synthesis are not clearly distinguished. This is especially in section IV C required.

7. For biological drug substances the same requirements are asked that are usual for biotechnological drug substances. There is no scientific reason for this requirement.

8. Very often expressions have such a lag of precision that it causes uncertainties in legal requirements. For instance in section IV C no definition of "sufficient information" is given for the evaluation of the safety and quality of a drug substance by FDA.

9. In contradiction to the pharmacopoeia common methods such as titrations are only accepted with justification. We do not see a justification for this requirement. See comment on line 1384 in the specific comments.

Specific comments

Aside from the general comments the document would benefit from consideration of the additional comments listed in the following table.

High priority: additional comments relating to complexity of the manufacture and documentation e.g. Scope of Guidance, Flow diagram, Description of the Manufacturing Process and Process controls, Controls of Materials, Critical Steps and Intermediates; Characterization; Control of Drug Substance; Container Closure System.
Documentation required is partly more detailed compared to EU regulations.
Redundancies in different chapters should be avoided.

Recommendations for revision are concentrated on critical issues.

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Line Number	Draft Guidance Section	Comment	Rationale
General	The scope of the guidance should be reduced to NCE as in ICH M4Q.		
General	When referencing another section of this guidance or a section of the CTD, include the section descriptor along with the section numerical reference for a more informative cross-reference.		
27	I. Introduction	Delete "... and abbreviated new drug application (ANDA) ..."	The scope should be reduced to NCE as in ICH M4Q. API for ANDAs are well characterized with regard to quality safety due to their long market history.
59, 60	I. Introduction	Synthetic Peptides and synthetic oligonucleotides should be included	Synthetic peptides and synthetic oligonucleotides are produced by standard chemical reaction steps; the materials employed are well-characterized standard materials. Thus, no biological system is involved for generation of these molecules. Accordingly, they should be treated as chemicals.
81	I. Introduction	Add sentence "In particular, application of risk assessment principles, which are in line with FDA's Risk Based Approach, can justify a different approach."	Need to refer to the FDA policy, and allow application of RBA principles
217	II. Background	Delete "volume and page number of the MF,"	In general the applicant does not know the volume and page numbers of an US-DMF.
237/8	II	Delete "and any contract facilities that are used (e.g. intermediate manufacturers, laboratories)"	It does not matter, who is involved in the manufacturing of the API as long as all requirements of GMP related to Q7A are met and the DMF holder has committed to do so.
281 - 282	II. Background	Methods validation package for API should be included in S.4.	Follow ICH M4Q

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Line Number	Draft Guidance Section	Comment	Rationale
363 - 365	II. Background C. (S.1.3)	Change "Detailed information on the characterization .....of these and other physical forms and conditions required to produce one form or another should be provided." to "Detailed information on the characterization .....of these and other physical forms should be provided."	In many cases it might not be possible to produce every single modification in pure form due to e.g. hygroscopicity, instability etc. Studies to produce modifications can be reported.
379	IV Manufacture	Add: "manufacturing (starting with API-SM) ..."	The most important SM is the API SM and the supplier should be relevant for the submission. In case of other raw materials a supplier qualification is a GMP aspect but not relevant for submission.
381 - 393	IV Manufacture A (S.2.1)	Delete the detailed information to "The name, address, and manufacturing responsibility should be provided for each firm (including contract manufacturers and testing laboratories) and each site ..... when the application is submitted to FDA"	Detailed information requested concerning contract manufacturers, testing laboratories, manufacturing buildings, room numbers of processing areas should not be part of the CMC information, but presented during site inspection (see also information required in appendix X.A.1).
406	IV Manufacture General	The Flow diagram should not include so many details. Process controls, operating parameters, expected yields are thoroughly described in the narrative part, and should not be repeated here.	Take care for the European requirements for Applicants Parts in DMF dossiers. Flow diagrams with detailed information are in contradiction to the confidentiality.
409 - 412	IV Manufacture B. (S.2.2)	"The entire manufacturing process should be depicted (i.e. **API starting materials** through drug substance release testing)." See Attachments 1 and 2 for information on **API starting materials**	For clarification please use the wording **API starting material** based on ICH Q7A.

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410	IV.B.1. Flow Diagram	General: Flow diagram must be simple Delete... "release testing"	In the flow diagram the synthesis and that means the production steps are described, but release testing is not a production step. Therefore it is not necessary to indicate that as a single step in the flow diagram.
417	IV.B.1. Flow Diagram	Delete..."drug substance release testing"	This is not a production step. Therefore it is not necessary to indicate that as a single step in the flow diagram. Redundancy with Chapter VI
425	IV.B.1. Flow Diagram	Delete..."auxiliary materials"...	Redundancy with B Description of Manufacturing Process and Process Controls
426	IV B.1. Flow Diagram	Delete..."critical process control"...	Please clarify critical process control and the points at which they are conducted. It is not a requirement in the EU CTD. CPMP/QWP/130/96 <Guideline on Chemistry of the New Active Substance> Redundancy with Chapter IV.B.2
427	IV. B.1. Flow Diagram	Should state only critical operating parameters (as with the process controls) particularly for this section on the Flow Diagram.	Recommend that process parameters be part of the narrative description rather than flow diagram...or give example of more critical process parameter that would be useful on the flow diagram.
431	IV.B.1. Flow Diagram	Delete "Yield":	It seems to be redundant to have the yield information in two places, see narrative text.
434-435	IV.B.1. Flow Diagram	Change..."each component"... to main components of the mixture should be indicated in the flow diagram.	Impurities are discussed in Chapter V.B. Main component would indicate e.g. those reflecting stereochemistry.

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443 - 445 457 - 458 and 521-522	IV.B.2. Description of the Manufacturing Process and Process controls	Change ..."all process controls".. to "**Critical** operating parameters and process tests" Delete ..."and the associated numeric ranges, limits, or acceptance criteria... Furthermore, any process controls...highlighted." Change ..."All process controls...should be included in the description of the manufacturing"... to "**Critical** operating parameters and process tests" It should be stressed that "*critical*" means "*critical for the quality of the drug substance*"	It is not necessary to describe the intermediate test, post-synthesis material test, unfinished drug substance tests and the associated numeric ranges, limits or acceptance criteria, because all this is described in chapter IV.D. (according to CTD requirements) To list and/or to describe **all** process controls is not necessary, but increases regulatory burden. The process controls listed/described in the dossier should be those that have been demonstrated to be essential to monitor and adjust the process, in order to guarantee the quality of the final drug substance. There are tests and controls are currently performed during the process only to gather data on the process in case of future need of investigation. It is not necessary to mention in the application **all** process controls. Too many details leads to more effort in change amendments on both sides, authority and applicant. Therefore manufacturers will reduce their efforts of monitoring. That will increase the risk for the product quality.
449	IV.B.2 Description ...	Change "A detailed description of each manufacturing step" to "... of manufacturing of each intermediate"	Detailed reasons needed Recommendation: Suggest that a cross-reference to lines 1753-1757 be made here for the definition of "step". The step is defined as in lines 1753-1757, where a reaction step is followed by several purification steps, therefore it should be used the term intermediate

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459	IV B.2. Description ...	Delete this sentence "Type...(e.g. HPLC) used for each process test..."	The full description of in-process material tests is given in Chapter IV.D. that includes process tests that are critical.
469-470	IV.B.2. Description ...	Delete ", and the disposition of unused fractions"	Unused fractions have no effect on the quality of the Drug substance.
466-467 and 630	IV.B.2.. Description and 3. Recovery	Delete this sentence..."Identification of manufacturing steps..." Delete this sentence .. "The use of recovered solvents ...of the manufacturing process."	This requirement indicates that we should distinguish between recovered and other solvents. As recovered solvents and auxiliary materials are always used according to their adequate specification. This differentiation is not needed.
471-472	IV.B.2.. Description	Delete this sentence..." Identification of processes..."	Due to the submitted ranges of in- and out-coming material of each manufacturing process there are different batch sizes that have to be combined according to production conditions. It is common understanding that all batches can be combined if these are in specification. (see ICH Q7A Chapter 8.4)
488 and 1520-1528	IV.B.2. Description	Change ..."A statement should be provided. .are not used in the same facility." to "A risk assessment to prevent BSE contamination should be provided."	As the BSE risk is determined by the material, the process and the risk of cross contamination conducting a specific risk assessment in any case of animal origin material would insure low BSE risk. Therefore, focusing on BSE countries only would not be sufficient.

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496 - 498	IV.B.2. Description	Significant *Differences between the manufacturing process described in S.2.2. and the manufacturing process used to produce the primary stability batches should be discussed in S.2.6.*	Adoption to wording in line 908.
508 - 509	IV.B.2. Description - Process Controls	Operating parameters...(e.g. temperature...) General Comment: Please replace process test by process monitoring	It is not reasonable to include all operating parameters, in particular for automated facilities. It should be limited to critical operating parameters. Among all process controls, only critical controls should be described (see also comment No. 443-445) Clearly differentiation from process controls (all tests within the synthesis)
510 - 511 + 769	IV.B.2. Description - Process Controls	Delete "Environmental controls – conditions .... clean room classification)"	The Environmental control is only important if the material is handled in an open area, therefore it is not necessary to submit all room classification. These data should be considered as part of GMP, and not part of the regulatory file
538 - 539	IV.B.2.. Description - Process Controls	Delete the sentence: "... all critical process parameters should be identified as critical on the flow diagram."	Redundancy with IV.B. and it is not necessary to have this information in the flow diagram and in the narrative text also.

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538-543	IV.B.2.. Description - Process Controls	Delete this section..."All of the operating parameters..."	Redundancy with IV.B. It is not necessary to describe the intermediate test, post synthesis material test, unfinished drug substance tests and the associated numeric ranges, limits or acceptance criteria, because all this is described in chapter IV.D.
541	IV.B.2. Description - Process Controls	"Tests on intermediates required to ensure the quality of the final drug substance" should replace "*All* tests on intermediates".	Only those tests and controls should be part of the file that have been demonstrated, using appropriate scientific methodology and risk assessment, to be critical. Additional data do not lead to improvements, but will enhance regulatory burden.
577	IV.B.3. Description – Reprocessing ...	Introducing unreacted material back into the process - ICH Q7A 14.22 - should be included here.	In addition, it should be stated that nonchemical enabling steps that are necessary to reintroduce the material into the established process, such as dissolving it in the original solvent, or filtration to eliminate unwanted solid materials, are allowed.
578 - 579	IV.B.3. Description – Reprocessing ...	This is a new definition for "rework" that is not consistent with ICH Q7A.	The definitions of reworking and reprocessing of ICH Q7A should be applied.
578-579 and 605-607	IV.B.3. Description – Reprocessing and Reworking	Delete this sentence..."Repetition of multiple reactions..."	This is in contradiction to the ICH Q7A. There is no differentiation between single or multiple reaction steps or unique or repetition use. It is only important that these steps are not different to the described process. Even for normal reprocessing the reintroduced material is slightly different as normal educts.

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611 - 616	IV.B.3. Description – Reworking	In general,...post approval...	If the reworking is not a single event the application is updated. It is not necessary to submit reworking which is used only once in the life cycle of product. In case of unique reworking the procedure is part of the failure investigation that is not relevant for submission.
620 - 643	IV.B.3. Description – c. Recovery	Delete the chapter c. Recovery	Recovery is a GMP activity and should not be part of the synthesis description. Only in case of a non-standard process, the description can be required here. Only specification of solvents (no difference between virgin / recovered solvents is necessary) and other materials are important for submission.
630 - 636	IV.B.3. Description – c. Recovery	Delete this sentence..."The use of recovered solvents..."	The quality of virgin solvent or recovered solvent must be the same and appropriate for intended use. It is a general issue in ICH Q7A Chapter 14.4
637	IV.B.3. Description – c. Recovery	Change..."Appropriate specifications for recovered solvents.." to "Appropriate specifications for solvents ..."	The specification must be valid for both types of solvents.
639 - 643	IV.B.3. Description – c. Recovery		The data on the number of times of recycling filtrates should be provided only when critical. These data are not applicable for continuous processes.

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645-653	IV.B.3. Description – d. Regeneration	Delete the chapter d. Regeneration	As above: this should be regarded as standard GMP handling – only in case of non-standard processes, – only specification of solvents (no difference between virgin / recovered solvents is necessary) and other materials are important for submission.
659 - 662	IV.B.3. Description – e. Other Operations	Repurification of aged material by reprocessing should be allowed – eliminate these lines	Appropriate validation being addressed, there is no additional risk; accordingly, there is no reason to treat this different from other reprocessing.
688 - 689	IV.C Controls of Materials	Suggest that the statement should be that "for synthetic drug substances, the starting material and the API starting material *are* the same."	Definition of Q7A should be accepted.
689 - 691	IV.C Controls of Materials	Clarification requested	Can the compound extracted from a natural source be a "starting material" for a semi-synthetic drug substance? If so, where is the information on the control of this starting material discussed? Line 689-691 references an "API starting material (extract) while in line 2001 and 2079, extract is called an "intermediate".
697	IV.C Controls of Materials	Include "Drug substances described in official compendia"	API described in the USP or European Pharmacopoeia fulfills all quality relevant criteria and should be acceptable.
698 - 701 1681 - 1683	IV.C Controls of Materials	Delete the sentence.	Term "sufficient information" is not precise enough to avoid legal uncertainties. Take ICH Q7A for choosing API SM.
713	IV.C Controls of Materials	Clarification requested	More clarity should be provided on what should be included in the flow diagram: Does this apply to the starting material or to the drug substance?

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726	IV.C Controls of Materials	Change "TSE" to "BSE"	In accordance to the risk assessment to BSE in line 489.
769 - 777 and 780	IV.D. Controls of Critical Steps and Intermediates	Delete this section..."or unfinished drug substance"... Delete this part..."and a brief description of the test provided."	Only critical process controls and associated ranges/ limits should be listed in the beginning of the justification. To many details increase the efforts for change amendments. Please clarify differentiation between "intermediates" and "Critical (key) intermediates" Compare to Chapter 3.2.S 2.4 of EU-CTD requirements The name of the process control should be sufficient.
780/1	IV.D. Controls of Critical Steps and Intermediates	Delete sentence.	Definition and rational for critical parameter is part of the validation documents.
785 - 788	IV.D. Controls of Critical Steps and Intermediates	This information should be requested only for a new drug substance.	---
807 - 810	IV.D. Controls of Critical Steps and Intermediates	The limits for in-process-controls need not to be tighter than the release limits.	Cleaning of substance in subsequent steps possible.

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810 - 812	IV.D. Controls of Critical Steps and Intermediates	Change ""Test performed in-process in lieu of testing the drug substance should be included ... and the results of such tests should be included in the batch analysis reports (e.g. certificate of analysis)." to "... and the results of such tests should be marked in the batch Analysis (S.4.4)	Reference to Certificate of Analysis here should be clarified, these are not necessarily in CTD section S 4.4 Batch Analyses. CTD section S.4.4 can be tabulated data for organizational purposes.
818	IV.D. Controls of Critical Steps and Intermediates	Delete "assay"	Assay testing is not always feasible and/or necessary.
839 - 864	IV D. Controls of Critical Steps and Intermediates	Rename "Post-synthesis Material" and "Unfinished DS" into "Pre-DS Material" to have only one category.	To simplify the process and to be harmonized with ICH Guide Q7A The need to have a differentiation between "Post-synthesis material" and "Unfinished Drug Substance" is unclear. The same information seems to be required for all these materials. There should be only one category of material after the final intermediate and before the final drug substance, if any. There is no need for defining special classes like post synthesis material or unfinished drug substance (there are no different GMP or regulatory requirements defined for these types of materials, see also lines 2134-2139 and 2184-2191).
General	IV.E. Process Validation and IV.F Manufacturing Process Development *General comment: It should be mentioned that these sections apply only to new drug substance (not marketed yet)*		
900 - 903	IV.F. Manufacturing Process Development	These studies should be cross-referenced with pharmaceutical development in section P .	

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905 - 910	IV.F. Manufacturing Process Development	Please clarify primary stability batches	Are these the batches for early stability testing in the clinical trial faces or are these initial ICH stability testing?
931	V. Characterization	Delete "... counterion stoichiometry, regiochemistry .."	If not, please clarify requirements for counterion stoichiometry and regiochemistry
986 and 988	V.2. Physico-chemical Characterization	Change to: ..."A summary of these investigations should be included, if applicable".	If there are no other solid-state forms there is no need for further stability studies and therefore no requirement for a summary report. Does this apply also for APIs used in liquid dosage forms (e.g. as solutions)? A summary should be dispensable in case that no interconversion was observed during stability studies.
1008-1016 1031-1035 1037-1040	V.B. Impurities	Revise the total chapter B Impurities to the focus on related substances	This chapter should focus on two types of related substances (organic impurities): potential and actual found impurities. The other types of impurities (e.g. inorganic, residual solvent) are discussed in the chapter VI.E. according to ICH Q6A.
1059-1060	V.B. Impurities	Delete: "Summary of the route of synthesis or method of preparation..."	Usually, proof of structure is provided and should be sufficient. If the impurity is characterized, what is the added value of providing the route of synthesis?
1063	V.B. Impurities	Change " ..a table listing the "qualified level of expected impurities .." to "... qualified level of actual impurities... "	Delete expected: Replace by "actual" according CPMP/QWP/130/96 page 9

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1111-1114	V.B. Impurities	Delete this sentence	Test will be accepted from the supplier according to the status of the supplier certification, and according to continuous evaluation. This is not a constant process. Since the applicant has to guarantee compliance to the specifications in any case, this provision is unnecessary.
1117 - 1120	VI. Control of Drug Substance - A. Specifications	Delete this sentence..."Tests that can..."	The requirement that specification needs to indicate whether result stems causes necessity for numerous change applications.
1129	VI.A. Specifications – Table 1	Delete the acceptance "... crystalline powder .. "	This example might be misleading. Acceptance criteria for appearance "... crystalline powder ...", because it is not possible for most drug substance to determine "CRYSTALLINITY" by visual inspection.
1129-1130	VI.A. Specifications	***Typo error*** - Table 1: the example "*any unspecified* ***NMT 0.1%*** " is not consistent with ICH Q3A and lines 1785 and 1922 (NMT 0.10%)	---
1131	VI.A. Specifications – Table 2	Delete"... protein..." in the title or change to "... synthetic peptides ..."	Proteins are not part of the scope of this Guidance, see page 2
1141	VI.A. Specifications	Periodic Quality Indicator Tests PQITs are welcome in practices, but not favored in dossiers.	PQITs will be soon routine. That will last in extension of the release specification. Therefore industry will not apply PQITs if the are required in a dossier. That will increase risk in production.
1176	VI.A. Specifications	A batch failure due to technical reasons (failed valve, broken equipment or likewise) should be acceptable.	If the batch failure is caused by reasons not connected to the process, the PQIT is still valid.

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1205	VI.B. Analytical Procedures	Remark to "Official Compendium" (not only USP/NF).	It is industries expectations that other compendiums are include, e.g. EP or JP as well as other.
1219-1220	VI.B. Analytical Procedures	Because of global submissions, references to major regional compendia (i.e., Ph. Eur., JP, BP) should be acceptable (with or without providing a copy of the procedure). At least all compendia of the ICH regions should be accepted.	The requirement to provide the analytical procedure from another country's compendium (e.g., EP or JP) is not consistent with the principle contained in footnote 21, in which it is stated that citation of a compendium means the current revision of the cited compendial monograph is used. The requirement to provide the analytical procedure from another country's compendium would mean that the version of the analytical procedure (from e.g. EP) submitted in the NDA would become outdated as soon as the next revision of the EP is effective. We suggest that for analytical procedures cited from widely available national compendia (e.g., EP, JP, BP, etc.), it will not be necessary to provide the text of the monograph or analytical procedure.
1229 – 1230	VI.C. Validation of Analytical Procedures	Change "This information...for all analytical procedures ..." to "This information should be provided for all non-compendial, quantitative analytical procedures listed ..."	This sentence states that validation data should be provided for ALL analytical procedures. However, validation data, or at least FULL validation data, are not required for official compendial methods. It is current practice that such methods should not to be validated in any additional lab acc. to ICH Guidelines. Is it the expectation of FDA that a USP general method such a residue on ignition, heavy metal etc. be validated? Otherwise this could be interpreted that validation data should be needed for compendial test procedures in the dossier, too.

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1235	VI.C. Validation of Analytical Procedures	Validation of analytical methods for testing the quality of the API is only required.	Validation package of methods is not regional information, since it is requested by the other regions, too.
1241 and 1246	VI.D. Batch Analyses	Change..."Batch analysis reports (e.g., certificates ... COA)" to "Batch analysis data" - delete „reports"	It should be left to the discretion of the applicant in which format he submits the data.
1246	VI.D. Batch Analysis	Delete this part ."evaluate consistency in manufacturing "	This leaves too much room for interpretation; in the worst case this could mean to deliver data from the very early phase of development; those data may have been gathered with completely different analytical methods that raises other questions such as the one for validation.
1254	VI.D. Batch Analyses	Delete "Manufacturing process...applicable."	Redundancy to the development report IV.F.
1261 – 1278	VI.D. Batch Analysis Report	The two chapters "Batch Analysis Reports" and „Collated Batch Analysis Data" should be united under the header „Batch Analysis Data"; the word „report" should be avoided.	The term report may be misunderstood; as indicated previously in the text this may also be a CoA and not necessarily a formal working report.
1263-1265	VI.D. Batch Analysis Report	Clarification should be provided on "*tests that are not part of the proposed specifications*"	Are these tests applied during development studies and not eventually retained for specification? If it is the case, it should be clearly indicated that these tests are to be included only for development batches used in clinical trials.

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1263 - 1264	VI.D. Batch Analysis Report	Delete "..., including tests that are not part of the proposed specification."	Exclude process development batches. During process development many test are applied just to investigate the process. They are not relevant for the quality of the drug substance in all cases especially in early stages of the development. As per guideline FDA request that all testing including the one that are not proposed in the specification. Sometimes testing is performed for information only and do not appear in regulatory submission.
1267 – 1276	VI.D. Batch Analysis Report	Delete the paragraph, add the sentence: "A summary of any critical changes in the analytical procedures should be provided in chapter S.4.2."	Analytical Development is described in S.4.2; the CTD format foresees the submission of an Analytical Development Report, which covers the issues addressed in this paragraph. See also EU CTD (CPMP/QWP/130/96).
1310 – 1311	VI.E. Justification of Specification Tests	Delete..."one that was reported in the batch analyses"; add separate sentence: „It may also be appropriate to justify exclusion of tests reported in the batch analyses (S.4.4)."	As it is the text conveys that exclusion of any test performed on a clinical or toxicological batch would have to be justified. Such a request is deemed too strict.
1331	VI.E. Justification of Specification Tests	The proposed sunset test protocol is not attractive.	The approval process has to be explained.
1341	VI.E. Justification of Specification Tests	Please define "Reasonable allowance".	If the highest level of particular impurity was observed at 0 4 % level and qualified, is NMT 0.5% (25% higher) specification acceptable to FDA?
1372	VI.E. Justification of Specification Tests	This requirement is not traceable.	Process related limits would lead to tighter limits that are not justified by ICH Q3C.

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1384	VI.E. Justification of Specification Tests	This requirement is not acceptable.	The example excludes the use of e.g. titrations. They always would have to be justified. In contradiction this methods are established in pharmacopoeia. This leads to less redundant methods for determining e.g. purity or assay. The quality of the drug substance is less assured.
1401 – 1402	VII. Reference Standards of Materials	Delete the sentence..."A list of any available reference standards for impurities and intermediates..."	A reference standard is a substance of the highest possible purity, which has been carefully characterized with various analytical methods. It serves as a master for quantitative analytical determinations. For impurities and intermediates such a reference standard is not available. Therefore the requirement to provide a list of reference standards for impurities and intermediates should be deleted.
1412-1413	VIII. Container Closure System	Delete "For non-functional secondary ... should be provided."	What is the purpose of including a description of non-functional secondary packaging component? Only primary and secondary packaging components, when these are functional, should be described.
1414-1418	VIII. Container Closure System	Change..."The suitability of the container Closure System...and referenced in S.6." to "if the container closure system is critical for protecting and assuring the quality of the active substance the choice of the primary and secondary packaging material should be justified."	A description including specifications and detail of the materials of construction should be sufficient (see CTD EU requirements)

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1429 – 1434 and 1442 – 1447	IX.A. Stability Summary and Conclusions and IX.C. Stability Data	Please include a note that the requirements of chapters A. and C. may be provided together, e.g. in a report.	Often applicants provide actually stability data and the conclusion drawn from them together in one report. It should be made clear that this practice is feasible further on.
1465 – 1474	IX.C.2. Primary Stability Studies	Start the paragraph with: „If the analytical procedure listed in the stability protocol is different from the analytical procedure describe in S.4 a summary of any changes ..."	The paragraph should only be valid for cases where the analytical procedure applied for the stability studies is different from those described in S.4.
1490	IX.C.3. Stress Studies	Delete .."Any"	In early development orientating stress testing is performed. Only stress tests performed according to ICH Q1 are relevant for this section.
1553-1569 and 1594-1597	X. Appendix A	Delete this chapter for synthetic and semi-synthetic synthesis of APIs.	Inactivation is not necessary in case of subsequent chemical reaction. In 1567-1568 is explained that chemical reaction inactivates those materials.
1646 - 1651	XI. Regional Information C. Methods Validation Package	Please revise this chapter	Redundancies between R.3.S and S.4.3 should be avoided. Therefore only additional requirements should be clearly specified here.

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–General	**Starting Materials** ... Attachment 1: for synthetic APIs and Attachment 2: of plant or animal origin.	Replace Attachment 1 and 2.	We do not accept and understand the content of the attachment 1 "Starting Materials for Drug Substances" and would recommend the above-mentioned criteria and as well as the required documents defined in Attachment 2 (see General Comments on page 1-3). Attachments 1 and 2 do not give assistance to the industry but complicate the understanding of the FDA requirements. The required criteria are not in compliance with ICH-Guide Q7a
1676	Attachment I	This leads to an extension of the information and change control to parts of the synthesis that are not applied concerning GMP.	This is in contradiction to Q7A and leads too much increased efforts for change amendments for applicant and authority.
1683-1685	Attachment 1	Please cancel this sentence. ..."A drug substance that is used to synthesize another drug substance..."	A drug substance is a well-described material of very high quality. It should be acceptable to use a drug substance as starting material.
1689-1694	Attachment 1	Delete this part.	The manufacturing of a drug substance has to be done under well controlled conditions as already required by Q7A independent of the origin of the SM. Well availability warrants good quality.
1740-1751	Attachment I	Delete this part.	The rational for the propinquity does not reflect to the fact that additional reaction steps are an origin of additional impurities.
1764-1766	Attachment I	Extraction has to be considered like distillation or chromatography.	
1770	Attachment I	Delete this requirement.	This is a new requirement. Q7A does request a well-characterized substance.

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1777	Attachment I	Not acceptable	This requirement is in contradiction to the request for the commercially availability. Such availability is in most cases only of technical grade where origins of impurities are given.
1792-1797	Attachment I	Delete this part.	We do not understand the rational. With a TSE statement for the API there is now need to define the starting material at or before the point where TSE agents can be introduced into the process.
1799 ff	Attachment I		If a quality control by current methods can be proven a SM should be acceptable.
1807-1811	Attachment I	Definition not sufficient.	There is a lack of scientific arguments.
1811-1818 1964-1968	Attachment I	This definition will not last long.	The mentioned methods e.g. chiral HPLC are already established routine tests.
1875-1877	Attachment I	This is not practicable.	Not every supplier is willing to give this information. This could exclude a better SM quality for application.
1924-1926	Attachment I	Controlled impurities from SM should be allowed.	Toxical impurities are critical independent from the origin.
2038	Attachment II	In total not applicable	Only in very few cases it will be possible to provide such a list of pesticides and herbicides.
2049	Attachment II	What does that mean? Please clarify.	
2073	Attachment II	A "screening for pesticides and herbicides" is not necessary.	This will be covered by the impurity profile investigation.
To be added	Glossary	**Sunset testing** and **PQIT** should be added to the glossary	

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2110 - 2113	Glossary	Adventitious Agents AA are not relevant in chemical or semi-chemical synthesis. Delete "mycoplasma".	AA will be deactivated by chemical reactions. Mycoplasma is not an AA.
2134 – 2139 and 2184 - 2191	Glossary	**Drug Substance** and **Post synthesis Materials or Unfinished Drug Substance:** change to the definitions of **APIs** and **intermediate** in ICH Q7A	Harmonization with ICH-Guide Q7A is required. There is no need for defining special classes like post synthesis material or unfinished drug substance (there are no different GMP or regulatory requirements defined for these types of materials, see also line 839 - 864).
2141 - 2146	Glossary	Final intermediate: Change...chemical reaction "that produces the molecule or ion ..." to "... that produces the chemical entity or ion .."	The last chemical step does not necessarily lead to the desired physiological or pharmaceutical properties. It could be for e.g. stability, applicability, solubility, etc. reasons.
2145	Glossary	Final intermediate: Delete the bracket "... (including a salt with hydrogen or coordination bonds) ..."	That is not a scientific definition of a salt.
2160-2163	Glossary	Please quote properly	The "purification" in Q7A has been deleted (s.236 in Q7A).
2151 – 2153, 2168 – 2169 and 2171 – 2172	Glossary	**In-process Material Tests**, **Intermediate Tests** and **Operating Parameters**: Change to the definitions in ICH Q7A: **In-Process Controls IPC** or **Process Controls** "Checks performed during production in order to monitor and if appropriate, to adjust the process and / or to ensure that the intermediate or API confirms to its specifications.	Harmonization with ICH-Guide Q7A is required.

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2234 - 2339	Glossary	Change "Starting Material .. " to "API Starting Material is a raw material, intermediate, or an API that is used in production of an API and that is incorporated as a significant structural fragment into the structure of the API. An API Starting Material can be an article of commerce, a material purchased from one or more supplier under contract or commercial agreement, or produced in-house. API Starting Materials are normally of defined chemical properties and structure."	Harmonization with ICH-Guide Q7A is required. Drug Substance: Clarify that the term "Drug Substance" is identical with the term "Active Pharmaceutical Ingredient" as used in ICH Q7A.

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